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AN ANALYSIS OF ANESTHESIA DEATHS IN CHILDREN'S HOSPITAL FROM 1941–1945

Dr. David L. Cronin

This paper is an attempt to survey the anesthesia deaths at Children's Hospital during the 5 year period of 1941–1945. Quite obviously, not every death which occurs on the operating table is due to anesthesia. Some of the patients were in extremely critical condition at the time of surgery. Therefore, in analyzing the operative deaths, the cases will be discussed under 3 headings: (1) Those deaths probably due to the anesthetic; (2) those deaths probably not due to the anaesthetic and finally (3) those deaths which occurred during intracranial surgery. Each case in turn will be described under 3 divisions: (1) Brief description of the clinical aspects as well as the pathological report when available; (2) discussion of the probable mechanism of death and lastly (3) methods of preventing the recurrence of similar accidents.

I. DEATHS PROBABLY DUE TO ANESTHESIA

Case #1: A 9 month old female (P. A. B.) was operated on for a strangulated inguinal hernia. The patient ceased to breathe following the initial incision and shortly afterwards brownish fluid in large quantities was regurgitated. Autopsy revealed that a large amount of gastric contents was present throughout the lung.

Discussion: Death in this case was due to aspiration of gastric contents. The patient was operated on several hours following admission. The child had received no food while she was in the hospital but the intestinal obstruction had caused reverse peristalsis with regurgitation of intestinal contents into the stomach.

Whenever death occurs following the initial incision, one should think of ventricular fibrillation as a possible factor. This arrhythmia occurs most frequently with chloroform but occasionally with ethyl chloride induction. The ventricular fibrillation results not only from the direct action of the anesthetic on the heart but also from the discharge of epinephrine produced by premature surgical procedures.

Prevention: Preoperative patients should receive nothing by mouth for at least 5–6 hours prior to surgical procedures. If emergency surgery is imperative, particularly in a patient whose dietary history is unknown for the previous 7 hours, a gastric lavage is indicated. This procedure is extremely important as a preoperative precaution in any patient with intestinal obstruction where regurgitation through the pyloric sphincter may occur.

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Reflex vomiting is more likely to occur during the lower stage II of anesthesia than at any other time. Therefore surgery should not be attempted before the stage of excitement is over. If vomiting and retching do occur, the patient's head should be lowered and turned to one side and the pharynx aspirated.

Lastly, surgery should not be attempted prior to plane I of the 3rd stage as premature surgery may result in a sudden release on epinephrine into the blood stream with subsequent ventricular fibrillation. Ethyl chloride induction is the second most common cause of ventricular fibrillation.

Fortunately, death due to gastric aspiration was a rare accident at Children's Hospital as it occurred but twice in 13,000 cases where inhalation anesthesia was used.

Case #2: An 8 year old male entered the hospital for a routine tonsillectomy. The history and physical examination were essentially negative. Death occurred due to cardio-respiratory failure during the anesthesia induction before the operation began.

Discussion: The induction period in anesthesia extends from the first inhalation of the anesthetic to the beginning of surgical anesthesia. This period is undoubtedly the most dangerous interval in the anesthesia. The respirations are likely to be irregular and respiratory reflexes exaggerated. During the excitement stage of the induction period the patient is unconscious and can no longer cooperate, respiratory reflexes cause spasmodic inspiratory and expiratory arrest, coughing or alternating periods of shallow and rapid breathing. The respiratory irregularities result in an uneven rate of absorption of the anesthetic into the blood stream. After a period of apnea, the patient usually breathes deeply and rapidly so that a dangerously high concentration of anesthetic may be quickly reached in the blood stream.

Respiratory arrest, as occurred in this case, may have been due to an overdose of the induction agent, particularly in an apprehensive child. Two factors contribute to the arrest in breathing. First, the frightened child struggles and cries when the administration of anesthetic is started. Crying causes carbon dioxide to be blown off and thus diminishes the concentration in the blood of this chemical stimulant to the respiratory center.

Second, the ether is usually pushed in an attempt to rush through the excitement stage. The hyperpnea induced by the fright causes the concentrated ether vapors to be carried quite rapidly into the lungs, blood and brain. The central nervous system becomes flooded with ether.

Prevention: It is important that the induction period be conducted smoothly. If the character of the respirations permit, the child should be hurried through the second stage (again only if the character of the

respirations permit). If the patient holds his breath, the anesthesia should be lightened or the mask removed so that when respirations are resumed, a large amount of anesthetic vapor is not inhaled. The anesthesia should not be rushed if the breath is held.

It is generally stated that most anesthesia deaths occur during the second stage or the stage of excitement. Nevertheless in Children's Hospital, during the 5 year period, there were but 2 deaths during the induction period. Inhalation anesthesia was given 13,083 in this interval.

Case #3: A 9 year old male (R. H.) entered Children's Hospital complaining of epigastric pain. This was the patient's only symptom on the first day. On the following day, the patient was nauseous and vomited; the white count was 32,000. The physical examination was negative, tenderness and rigidity being absent. The fever rose to 103°. Death occurred during anesthesia induction prior to any surgical manipulations. An autopsy revealed rheumatic valvulitis and myocarditis.

Discussion: Abdominal pain frequently initiates a rheumatic attack, causing confusion in the diagnosis. The pain tends to be in the epigastrium, is not sharply localized with little or no tenderness or rigidity. Thus rheumatic abdominal pain may simulate an acute abdomen so that a laporotomy is performed.

With ether anesthesia, the cardiac rate is increased during the phase of induction mainly due to the release of epinephrine. The blood pressure also rises during this period. The increased rate and pressure result in an increased load on the heart and if the cardiac musculature and connective tissue are diseased and weakened, the sudden increment in work may produce acute dilatation and failure.

Prevention: Rheumatic fever is extremely protean in its manifestations and the classical manifestations are frequently absent. In all cases of abdominal pain, rheumatic fever should be considered in the differential diagnosis. Where rheumatic fever is considered as the etiology of the abdominal pain a therapeutic test with 100–150 grains of salicylates orally should be tried. Abdominal rheumatic pain usually responds to salicylates.

Case #4: L. W., a 3 year old male was operated on for a left inguinal hernia. The sac was dissected and amputated. Respirations ceased 5 minutes following cessation of anesthesia. Autopsy revealed acute dilatation of the heart and atelectasis.

Discussion: Massive collapse of the lung secondary to anesthesia is usually caused by shallow respirations and bronchial obstruction, particularly from mucous. Atelectasis is due to complete absorption of gases by the blood flowing through the lung distal to the occlusion of a main bronchus and occurs within a few minutes. It may not be noticed if

a closed system with high oxygen tension is being used. As soon as the anesthetic is stopped, as in our case, cyanosis and dyspnea became apparent and physical examination revealed evidence of pulmonary collapse.

The cardiac dilatation was probably secondary to the atelectasis which resulted in a sudden strain on the heart, especially the right side.

Prevention: Prevention depends on the maintenance of sufficient depth of respiration by inhalation of carbon dioxide vapor if necessary and vigorous hyperpnea induced by carbon dioxide at the end of each operation in which breathing has been shallow. Excessive mucous from bronchial secretions may be prevented by pre-anesthetic medication with atropine and scopolamine. In treating fully developed atelectasis, oxygen and carbon dioxide should be administered for an hour or longer and direct bronchoscopic removal of the mucous plug may be attempted if early evidence of improvement is not forthcoming.

Case #5: This is the case of C. N. who entered the hospital for a repair of an imperforate anus. Death in this case was due to asphyxia following aspiration of gastric contents.

Discussion: The death in this case was similar in etiology to that given for Case #1 above. In both cases there was some form of intestinal obstruction probably resulting in reverse peristalsis and regurgitation of intestinal contents into the stomach. In the first case, the intestinal obstruction was due to a strangulated hernia whereas in the second case, obstruction resulted from an imperforate anus.

Case #6: An 11 week old girl, K.C., had been put under ether anesthesia in preparation for intracranial surgery because of internal hydrocephalus due to occlusion of the duct of Sylvius. A blood transfusion was being given (while under anesthesia) prior to surgery and the patient expired during this procedure.

Discussion: According to the accepted physiological doctrine of Kellie and Munro, there is a constancy of cerebral volume. A reciprocal relationship exists between the volumes of blood and spinal fluid. The third substance within the dura, the brain matter itself, is under normal conditions assumed to remain of constant volume.

With hydrocephalus, the intracranial spinal fluid pressure is markedly increased due to the occlusion within the ventricular system. Ether administration will also cause a rise in the intraventricular pressure. The increased blood volume due to the administration of the blood transfusion probably caused an increase in the blood pressure. Since the intraventricular pressure and blood pressure are directly proportional it is likely that the blood transfusion itself contributed to a further rise in the cerebrospinal fluid pressure. This together with the ether superimposed upon

an occluded ventricular system with a pressure already elevated may have been the precipitating cause of death. The cumulative effect of these 3 factors produced pressure on the vital medullary centers resulting in cardio-respiratory failure.

Prevention: It probably would be preferable to administer a blood transfusion in a child with hydrocephalus prior to anesthesia. In this way the transitory elevation in blood pressure would not occur simultaneously with the elevated intraventricular pressure produced by the ether.

II. DEATHS PROBABLY NOT DUE TO ANESTHESIA

Case #1: B. C., a 2 year old male, entered the hospital following an automobile accident. X-ray revealed a fractured clavicle, a left hemothorax as well as a diaphragmatic hernia in the left thoracic cage. Death occurred during closure of the abdominal wall following repair of the diaphragmatic hernia.

Discussion: Diaphragmatic hernial repair presents a unique problem. For some unaccountable reason, repair of large diaphragmatic hernias occasionally result in a fatality of indeterminate etiology. Manifestations of prostration, including also respiratory difficulty and an elevated blood pressure and temperature are usually present. It is possible that the cause of death is associated with the marked increase in the intra-abdominal pressure incident to the reduction of the hernia and its repair.

Prevention: Prevention of the increased intra-abdominal pressure is impossible because of the very nature of the operation. However, certain precautions should be followed in the performance of diaphragmatic hernial repairs. Several days prior to the repair, the phrenic nerve should be crushed so that movements of the diaphragm do not interfere with the operative procedures and healing occurs more rapidly. Since a pneumothorax is automatically produced following release of the hernia, a positive pressure of anesthesia is usually advisable.

Case #2: A 10 year old colored male (E. V.) was undergoing an operation for fusion of the dorsal vertebrae (Pott's Disease). Collapse occurred while the patient was leaving the operating room following the fusion.

Discussion: The cause of death in this case was considered to be surgical shock following an autopsy which failed to reveal any evidence for the cause of death. Surgery produces secondary shock somewhat different from primary shock. In surgical shock, the onset of collapse may be delayed for 1–2 hours following the onset of surgery. Therefore, in any extensive surgery, particularly where bones are involved, one must be prepared for the appearance of surgical shock at the end of the operation or 1–2 hours after leaving the operating room.

Primary shock is believed to be due to hemoconcentration resulting from the leakage of plasma from the capillaries as a result of an undue permeability of their walls. In animal investigations in secondary shock, hemoconcentration is not a general finding and there is indication that plasma is removed from the circulation by becoming "locked up" or pocketed in minute peripheral capillaries rather than by leakage of the vascular system.

Prevention: Surgical shock can be prevented by the maintenance of the circulating blood volume by blood transfusions, the administration of fluids and the protection of the patient against cold and pain.

Case #3: W. W., a boy of 5, was brought to the hospital with a fracture of the skull and lacerations of the temporal lobe, following a fall of 4 flights of stairs. Death occurred during decompression of the left subtemporal region.

Discussion: Autopsy revealed extensive contusions and lacerations throughout the brain. These in turn were responsible for the development of edema which along with the hemorrhage gave rise to sufficient compression to cause death. It is unlikely that this was an anesthetic death.

Case #4: A 6 weeks old infant (B. B. O.) was brought into the hospital with signs of internal rectus weakness and clonic convulsions. Death occurred during a diagnostic pneumoencephalogram under ether anesthesia.

Discussion: There is a paucity of reports in the literature indicting anesthesia as a possible cause of death during pneumoencephalograms. Dandy feels that the real danger of this procedure is due to the increased intracranial pressure which results from irritation of the brain by the air. Frequently patients appear in the late stages of intracranial pressure. A little pressure from the air irritation added to that which is already present may cause coma and death. In Dandy's opinion a pneumoencephalogram should not be done in cases of suspected brain tumor unless the patient is prepared to have the procedure followed by operative intervention on the tumor itself.

III. ANESTHESIA AND INTRACRANIAL SURGERY

The remaining cases of anesthesia deaths may be discussed as a group since they occurred during intracranial or extracranial surgery and endotracheal anesthesia was used in all the cases. It is very difficult to say whether the death in these cases was due to the anesthesia wholly, in part, or at all.

There were 7 deaths under anesthesia which occurred during some form of cranial surgery. Three cases were microcephalics and in each case death occurred during the craniotomy and before the dura had been pierced.

A fourth death occurred in a case of internal hydrocephalus following ventricular drainage. Two fatalities followed removal of subdural hematomata. In the last case, death occurred following removal of a cerebellar tumor weighing 100 grams.

As noted above, it is most difficult to say whether death in any of these cases was due primarily to the anesthetic or to the surgery. Ether and oxygen was used exclusively in all 7 cases. It is possible that ether may not be the anesthetic of choice in intracranial surgery in view of the fact that prolonged administration of ether produces cerebral edema and increased intracranial pressure.

The most important factor in determining the course and success of the cranial surgery, second only to the control of hemorrhage, is the maintenance of a normal or low intracranial pressure.

It is important that blood pressure, pulse rate and respiratory rate be recorded every 15 minutes during intracranial surgery. In this way, the anesthetist can discern the signs of shock in its incipiency. The anesthetist must be familiar with the normal changes in these recordings which follow certain operative procedures. For example, the blood pressure drops slightly from avertin anesthesia, and then rises back to preoperative level following intubation. There is an additional rise during the incision and another during trephining. There is an abrupt fall following the opening of the dura and the fall is greater if the intracranial pressure was increased. Similarly the pulse and respiratory rate vary with surgical procedures. Familiarity with these physiological changes enable the anesthetist to detect the first signs of adverse changes.

Lastly, what efforts should be made at resuscitation when the signs of shock are imminent? Most anesthetists reject analeptics as useless in anesthesia resuscitation. The first anti-shock measure is to increase the oxygen percentage in the gas machine. The second step is to administer intravenous crystalloid fluids or preferably blood and plasma.

SUMMARY AND CONCLUSIONS

During the 5 year period from 1941–1945 there were 17 deaths which occurred under anesthesia in Children's Hospital. Of these 17 deaths, 6 were classified as fatalities probably due to the anesthesia, 4 of the deaths were probably not due to anesthesia while the remaining 7 fatalities occurred during some form of intracranial surgery. Deaths in this latter group were not classified into either of the first 2 groups because of the difficulty in evaluating anesthesia as the lethal agent in cranial surgery.

In the 6 cases classified as anesthesia deaths, the following 5 factors were presented as etiological agents:

1. Failure to aspirate gastric contents in 2 cases of intestinal obstruction;
2. Overdose of the induction agent in a crying, apprehensive child;
3. Misdiagnosis of rheumatic abdominal pain for an "acute abdomen";
4. Failure to discern signs of atelectasis during the operative procedure;
5. Administration of ether and a blood transfusion simultaneously to a child with an occluded intraventricular system.

In the discussion of intracranial surgery, 3 points were enumerated for improving anesthesia technique:

1. Substitution of ethylene oxide or nitrous oxide as the anesthetic agent in place of ether;
2. Periodic recordings of the vicissitudes of blood pressure, pulse rate, and respiratory rate every 15 minutes.
3. Adequate anti-shock measures at the first signs of collapse.

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CLINICAL ANESTHESIA IN CHILDREN

Dr. Edward B. Macon*

In the past 10 years throughout the United States anesthesia in children has progressed apace with anesthesia in adults. However, there are some definite physiological differences present in these 2 age groups, and only lately have anesthetists and manufacturers of gas machines been truly cognizant of them.

Difficulties of administering anesthesia in children are to a large extent the same as those of pediatrics in general. As diagnosis is more difficult in children, so the child's physical condition for anesthesia is harder to appraise, and this lack of proper evaluation may result in disaster to the patient.

Children vary more in their reaction to drugs of all kinds than do adults, and knowledge of these reactions is best obtained from long practical experience, case discussions and scientific research.

Long ago I gave up the use of morphine and atropine for premedication in young children. I have found tribromethanol and the barbiturates, with the exception of pentothal sodium, safer and more consistent in action. This latter drug we cannot recommend for children under 10 years of age for the following reasons:

1. Pentothal is a powerful respiratory depressant.
2. The respiratory depression in children is out of proportion to the abolishment of reflexes.
3. Once the drug is given, it is irreversible.
4. An even plane of anesthesia is almost impossible to maintain in children.
5. The amount of pentothal necessary in a given case is greatly out of proportion to the body weight of the child. This may well result in a prolonged recovery time.
6. While very sick children tolerate venipuncture well, the same cannot be said for the well child.
7. The surgeon is often exasperated by lack of relaxation and the occurrence of movement even though depressant amounts of the drug have been given the patient.
8. Bronchoconstriction caused by pentothal becomes much more important in children, for the respiratory exchange may be critically reduced.

*Attending Anesthetist Garfield Memorial Hospital and the Childrens Hospital.

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9. Lastly, nationwide reports show that the mortality rate in the use of sodium pentothal for children is high. Manufacturers, surgeons and anesthetists have therefore almost universally condemned the use of this drug for children.

Avertin is peculiarly suitable for children as a basal anesthetic agent. It allays apprehension and quiets frightened, nervous children. Youngsters requiring multiple operations have requested rectal anesthesia for subsequent surgery. It has been found necessary in my series of cases to give larger doses of the drug to children because of their increased metabolism. While solutions of avertin have been given with a maximal one hundred and twenty milligrams per kilogram of body weight, one hundred milligrams has been adopted as the optimum dose for the majority of cases. Older children receive eighty to ninety milligrams per kilogram. As with adults under basal avertin, the amplitude of respirations is decreased and the rate is little affected, but may be slightly increased. Subsequent supplementary inhalation anesthesia is administered for the required depth of anesthesia and proper control of respirations. Avertin has little effect on the pulse rate. In an agitated juvenile with increased pulse rate, the rate usually diminishes toward normal. The pupils will gradually contract, and when fully contracted maximum effect is considered to have been reached. Except under decided sensory stimulation, the pupils remain contracted until the drug is detoxified and consciousness is regained. Dilatation from sensory stimulation occurs only under light anesthesia. The average child is asleep eight and one half minutes after avertin has been given while the average recovery time has been one hour and sixteen minutes. Induction seems to be shorter and recovery quicker in children than in adults.

When I first began the use of avertin, it was found that the greatest difficulty was having the child retain the fluid. This can largely be prevented if the tube is allowed to remain in the rectum and kept elevated until the child is asleep. If this is done, any tendency to expel the solution results only in forcing it momentarily up the tube and none is lost, provided strict supervision of administration is practised. Occasionally a child expels a small amount after reaching the operating room, but sufficient avertin has been absorbed so that the loss has no appreciable effect on its anesthetic action. A large size male catheter is used, connected by a glass tube to about 3 feet of rubber tubing attached to a small funnel. The glass connector indicates whether the fluid is being forced back and the length of the tubing will provide sufficient pressure, when elevated to overcome rectal resistance to the flow of the solution. A large rectal tube introduced in a child is more apt than a catheter to set up an expulsive

tendency. There is no advantage in injecting the solution high in the rectum, and the catheter should not be inserted more than 3 inches, otherwise it may double back, causing expulsion.

Now as to gas machines in children: The gas machines which I use for children are the closed, unidirectional, circular, absorptive type which are better for them than the to-and-fro type, since the latter has an increased dead space. I have used them with care on children who have had a tidal volume as low as 175 cc. As the dead space in the tubing and mask plus the physiological dead space in the respiratory tract of the child may exceed its tidal volume, it is obvious that serious carbon dioxide excess may occur. Carbon dioxide in excess often produces an uncompensated gaseous acidosis. We have even discontinued the use of the unidirectional circular absorptive machine in small children except in selected cases that are intubated so as to reduce physiological dead space to a minimum. For this reason open-drop ether is given to the small child.

Intubation decreases both the mechanical and physiological dead space. The physiological dead space is estimated at 150 cc., while the mechanical dead space has been estimated up to 200 cc. With the intratracheal tube in place, it is estimated that the cubic space in the tube is only 14 cc. As most of the gases are channeled through this tube, it can be readily realized how much the dead space is reduced. In addition to cutting down dead space, intubation practically eliminates the bad effect of malposition of the head and neck, allows free exchange of gases, facilitates insufflation of lungs with oxygen and removes the anesthetist from the field of operation, making adjustment of the head entirely to the advantage of the surgeon. It also greatly facilitates tracheobronchial toilet; excessive secretions can be easily aspirated from the trachea. Intratracheal intubation should be done whenever the pleural cavity is to be opened in order to prevent suppressed, inefficient or paradoxical breathing. By intubation a constant positive pressure can be maintained to expand the collapsed lung, due to the entrance of atmospheric pressure into the pleural cavity. The exceptions to this statement are governed by the age and size of the child and nature of the operation. The smaller the rima of the larynx, the more apt it is for any resulting edema to cause laryngeal obstruction and asphyxia. In children under 2 years of age, we weigh the possibility of any trauma to the larynx against the advantage for any given surgical procedure. In typing a ductus arteriosus in younger children, I have refrained from doing a tracheal intubation, as there is no pathologic condition of the lungs present.

Spinal anesthesia has been a great aid in certain cases where other agents might have produced untoward results. The dosage of 1 mg. of procaine

per pound of body weight has been adequate in my experience. In case of intestinal obstruction, diabetes and cardiac decompensation, this agent has seemed to be the anesthetic of choice. Spinal anesthesia has proved to be a valuable anesthetic when the administration is accompained with exercise of the usual precautions relating to height of anesthesia, blood pressure and pulse rate.

In administration of anesthesia to the child under 3 years, open drop ethyl-ether anesthesia is best from the standpoint of potency and safety. Furthermore mask administration conforms more closely to physiologic gaseous exchange. The agent should be delivered with a minimum of effort to the lungs. At the present time, although it will not be for long, ethyl-ether is the most valuable. It has these disadvantages:

1. It is an irritant to mucosa, stimulating secretions and facilitating development of atelectasis, which, however, can usually be prevented by using the suction catheter present in every operating room.

2. It may cause acidosis, albuminuria or hyperglycemia.

3. It increases intracranial pressure by dilating cerebral vessels, depresses the respiratory center and inhibits the action of the respiratory carriers in internal respiration. Respiration is stimulated by ether only through reflex stimulation of the respiratory mucosa. Although there are other disadvantages of a lesser degree, ether anesthesia remains the best for this age group.

Sometimes special problems occur in anesthesia for children. Recently the problem was encountered of anesthetizing a few days' old infant, who on account of subdiaphragmatic hernia, required positive pressure oxygen during the operation to prevent cyanosis. With a baby size face-piece, a close fit to the face was obtained, and oxygen was delivered under slight pressure. The intake tube was removed momentarily from the machine and small amounts of ether were vaporized in the tube itself. In this way the baby was kept at a fairly even level of anesthesia for one hour.

Effects of the emotions on the body metabolism are factors which greatly influence the conduct of the administration of anesthesia to minimize psychic trauma. It is desirable to place a patient in the optimum psychic state together with other essential preparations for operation. Panic or depression preoperatively makes the patient a poorer operative risk. After operation the patient is occasionally unable to make satisfactory psychic adjustment. This complication may take the form of a psychosis or neurosis. Mild sedation is inadequate since conscious control over fears is often lost and the patient becomes even more unmanageable. Phychic trauma caused by unguarded remarks or hurried attitude of hospital personnel should be guarded against. Induction of anesthesia in children, properly administered, should be uneventful and should not

precipitate terrorizing memories that remain as a permanent fear for any subsequent anesthetic experience. It is the contention of some anesthetists that the anesthetic process should be explained to children before operation. To my mind it is doubtful if this is wise in the majority of instances. However, children old enough to understand what is meant by an anesthetic, even in its simplest meaning, may be instructed, but not by the parents. If the induction is carried out as outlined, there is nothing unpleasant to experience and hence any warning, or hint of unpleasantness, only adds to the natural apprehension at sight of the anesthetist, hospital personnel or apparatus.

The general conduct should be cheerful without too much talking. Attention by the anesthetists to the smallest detail is obviously highly essential in effecting successful induction. Habit in proper procedure, all cases being given the same attention, should give the experienced anesthetist an appreciation and understanding of what causes fright among children in the ordinary nitrous oxide induction procedure.

Three troublesome features which are common in the induction of children and all of which prevent smooth induction are darkness, the smell of ether and restraint. In the first instance, the shield should never be placed over the eyes until after induction. This is a common mistake that tends to frighten the child at the onset. The second is the smell of ether. With the flow of gas the child may thus be made interested in something new and strange, and while forgetting his fears, the anesthetist is freer to ascertain by his olfactory sense that the machine is free from ether and other odors. Nitrous oxide, almost odorless, even if with a faint, sweet smell, should be allowed to flow until all other odors are supplanted.

The face-piece may now be held in plain view so that the patient can see that it is nothing to be feared. It should then be lowered until the gases are passing over his face to the partial exclusion of air. Anesthetization of the child can often be accomplished without the mask being held close to the face.

As nitrous oxide is heavier than air, it passes over the face, and to a large extent displaces the air. Ether may be added to the gases after signs of a light anesthesia are present. The attitude of the child is more often than not a reflection of previous training.

Avertin and certain barbiturates are a blessing to these spoiled and otherwise excitable children. If sufficient attention is given to the small details of induction, premedication will be often unnecessary.

SUMMARY

The following aspects of anesthesia in children might well be recognized:

1. Difficulties in physical appraisal.

2. Reaction to drugs due in part to increased metabolism.

3. Anatomical differences as exemplified by smallness of the tidal respiration in relation to the dead space of anesthetic machines with non-elimination of carbon dioxide.

4. The great advantage of intubation in eliminating dead space, and the use of positive pressure.

5. The art of induction in minimizing psychic trauma.

HYDRONEPHROSIS

Case Report No. 70

Dr. Charles Stiegler D. S. 43-3208

D. S., a 10 year colored male, was admitted to Children's Hospital on July 14th because he passed two grossly bloody urines the evening of admission. There was no frequency nor pain on urination. The patient had been hit in the region of the left kidney with a softball about six hours prior to the appearance of the hematuria, but the blow was not hard and caused no concern at the time it occurred. The past history and family history were unrevealing.

Physical examination on admission showed the abdomen to be soft, without tenderness or rigidity; no masses were palpable. The remainder of the physical examination was essentially negative. The temperature was normal; the blood pressure 120/80. The primary diagnosis was gross hematuria due to a possible kidney injury.

Repeated urinalyses during the first week showed innumerable red blood cells with no other significant abnormalities. NPN was 35 mgm%. The sedimentation rate was slightly elevated, and hemograms were normal except for a mild anemia. On July 17th, 3 days after entry, radiographic examination of the genito-urinary tract was made after intravenous injection of dye. The films were interpreted "as suggestive of traumatic injury to the left kidney, although hydronephrosis on the left side could not be ruled out." During the first two weeks of hospitalization, the temperature ranged between 99° and 101°, while the blood pressure remained essentially within normal limits. Successive urinalyses after July 25th failed to show any further evidence of hematuria.

A retrograde examination of the urinary tract was made on July 29th, revealing a marked hydronephrosis on the left side. Following this examination, there was a gradual rise in temperature to 104.6° on August 1st, at which time penicillin and sulfonamide therapy were administered. The temperature returned to normal within 24 hours, and the patient was continued on chemotherapy while being prepared for surgery.

On August 9th, a left nephrectomy revealed a large cystic kidney about three times the normal size. There was an obstruction at the ureteropelvic junction, probably due to a congenital stricture. On sectioning the kidney, the pelvis and calices were markedly dilated with almost complete absence of the normal renal parenchyma. Subsequent microscopic examination of kidney sections revealed the presence of subacute pyelonephritis.

The postoperative course was uneventful and the patient was discharged from the hospital two weeks after operation.

DISCUSSION

Dr. Hilbert S. Sabin: This case is of particular interest in that it illustrates the susceptibility to minor traumatism of kidneys in which there is pre-existing disease. The normal kidney, protected as it is by the heavy abdominal muscles and the bony thorax, is, in most instances, immune to trauma with the exception of direct violence of considerable severity. In this case, the blow sustained was of negligible force and caused no concern at the time. It was followed, however, by the passage of grossly bloody urine, which led to the patient's hospitalization. History and physical examination at the time of admission failed to reveal evidence of pre-existing renal disease or of possible renal rupture. The patient was treated expectantly and the hematuria gradually disappeared. An intravenous urogram demonstrated a poorly functioning, hydronephrotic left kidney, while the right kidney was shown to be normal in all respects. A cystoscopic examination with catheterization of the left ureter was then performed, and an impassable obstruction was encountered in the region of the uretero-pelvic junction. A retrograde pyelogram established the diagnosis of severe left hydronephrosis, apparently due to a stricture of the upper ureter. This was borne out at the time of operation, when a dense congenital stricture at the uretero-pelvic junction was encountered. The kidney was greatly enlarged, and the cortical tissue almost completely destroyed by hydronephrotic atrophy. It was obvious how direct trauma, even of a minor nature, might be a cause of hematuria in this situation.

This case emphasizes the importance of a careful urological investigation of all cases of hematuria secondary to renal trauma. Not infrequently, a trivial injury will call attention to pre-existing renal disease which had previously escaped detection.

OSTEOFIBRO-CHONDROMA OF THE SCAPULA IN A NEW BORN INFANT

Case Report No. 71

Dr. Ralph Stiller J. Y. 46-6488

J. Y., a two month old white female, was born after a normal nine month gestation. Birth weight was 7 lbs. 4 oz., neonatal period was entirely normal. The child was bottle-fed and received cod liver oil and orange juice in adequate amounts. At the age of 4 weeks the child's mother noticed that it was not using its left arm. At the age of 5 weeks an x-ray of the arm was taken and reported negative. For the 2 weeks preceding admission the child used her arm normally. At the age of 7 weeks, one week prior to admission, the mother noticed a mass on the left scapula that extended under the arm, was non-tender, and seemed to enlarge in the ensuing week. Past history was entirely negative for any other illness, the child eating and gaining weight well. Family history was non-contributory.

Physical examination on admission revealed a well developed, well nourished white female of 8 weeks in no apparent distress. With the exception of the local condition the physical examination was entirely negative. Locally there was present a hard bony mass that bulged behind the left shoulder, seemingly replacing the scapula. The mass was not tender, not red, and did not differ in temperature from the surrounding structures.

X-ray taken the day of admission revealed the presence of signs of destruction and bone formation in the scapula suggestive of osteogenic sarcoma. (Figure 1). Examination of the skull and long bones failed to reveal any evidence of metastases or any other abnormality. Urinalysis was negative. The red blood count was 2.8 million with nine grams of hemoglobin. There were 6,700 leucocytes with 49% polymorphonuclear cells, 45% lymphocytes, 3% eosinophils and 3% monocytes. There was a moderate degree of achromia, microcytosis and anisocytosis. Blood Kahn was negative. Serum phosphatase was reported as acid 3 King-Armstrong units (normal less than 4), and alkaline 17.6 King-Armstrong units (normal 6–20 in children.) Serum phosphorous was 3.2 mgms. and calcium 12 mgms.

A biopsy was done on the mass and the final report was osteofibro-chondroma containing bone, cartilage and fibrous tissue indiscriminately mixed. There was no evidence of malignancy.

DISCUSSION

This case is being presented because of the unusual occurrence of this rather common tumor in a patient so young and in a bone so seldom affected. The x-ray which gave the appearance of both an osteolytic and osteogenic process further complicated the picture so that it was with

Fig. 1

some surprise that the final pathological diagnosis was received. During the pre-biopsy consideration of the patient, Dr. Geshickter stated that although the picture strongly resembled osteogenic sarcoma it would be extremely unusual for this tumor to occur in one so young.

Osteogenic sarcoma usually occurs in the long bones, preferably in the lower femur or upper tibia, usually at the time of puberty. It is subperiosteal in location in the region of the metaphysis of the affected bone and by its production of new bone in a radiating manner from its point of

origin produces the classical sun-ray spicules associated with periosteal elevation and some destruction of the neighboring shaft. Pain followed by dysfunction of the part are almost always present.

Osteochondromata are usually multiple, and are congenital in origin even though due to their slow and at times arrested growth they may not be discovered until the age of 25. They occur near the ends of the long bones, are hard and nodular and relatively symptomless. The typical x-ray picture is one of a cauliflower-like mass with a lobulated translucent top beneath which there is an osseous pedicle fusing with normal cortical and cancellous bone. It is rare outside the long bones and pelvis. It may occasionally occur in the occiput, spine and scapula. They are usually harmless but may be excised, care being taken to remove the whole mass, if they become too large.

Ewing states that chondroma of the scapula has been described, that it may originate from various portions of the bone and that it may exhibit the structure of either benign chondroma or chondrosarcoma.

It seems highly likely that on a purely statistical basis when a tumor involving the scapula appears in a newborn infant benign chondroma or osteochondroma is the most likely diagnosis. However, a biopsy should be taken and in the rare event of malignancy a total excision should be done followed up by radiation therapy depending on the exact nature of the tumor mass.

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CLINICOPATHOLOGICAL CONFERENCE

Directed by: Dr. E. Clarence Rice

Assisted by: Dr. Lois Murphy

Case Report No. 72

Dr. Lois Murphy T. W. 44-4120

T. W., a 3 week old colored male, entered the hospital because of vomiting and generalized muscular twitchings.

The infant had apparently been in good health until 3 days before entry, when vomiting began, associated in 48 hours with muscular twitchings and irritability. At the onset of vomiting the patient had been seen in the dispensary where the positive findings were a slightly elevated temperature (101° rectal), equivocal nucal rigidity and abdominal distension. The formula had been modified and the mother instructed to return with her child if no improvement was noted.

The therapy instituted failed to benefit the complaints and the vomiting had become persistent without relationship to food. The infant apparently could not sleep and cried continuously. Generalized muscular twitchings were noted and there were transient periods of hyperextension of the spine and lateral deviation of the eyes and tongue during the 24 hours prior to admission.

Antenatal, natal, and postnatal factors were normal and the family history was non-contributory. The birth weight was $7\frac{1}{4}$ pounds. The infant's feeding consisted of breast milk and a supplemental evaporated milk formula. After an initial weight loss, the birth weight was regained by the seventh day, the weight increment being progressive up to the onset of this illness.

The physical examination on admission revealed a well developed, well nourished colored male infant, appearing about the stated age, very irritable and apparently acutely ill. The anterior and posterior fontanelles were found to be patent and bulging. The crown-heel length was fifty centimeters, the head and chest circumferences 34.2 and 33.7 centimeters respectively. Slight nuchal rigidity was detectable and was associated with hyperextension of the spine. Deep tendon reflexes were hyperactive, but the superficial reflexes could not be elicited. The eyes, ears, nose and throat were considered normal, while the heart and lungs were physiological. The abdomen was uniformly distended and the superficial veins were visibly engorged. Manual palpations of the underlying structures was deemed unsatisfactory because relaxation could not be obtained. Shifting dullness, however, could be demonstrated in the flanks.

The temperature was 98.6°. The weight was seven and one half pounds. Ophthalmoscopic examination revealed the discs to be flat, the margins being distinct and the vessels considered normal.

Examination of the blood revealed 10 gm. of hemoglobin, and a white-cell count of 10,600, with 38% neutrophils of which 13 were bands forms. The urine was cloudy, positive for albumin and microscopically showed many white cells in clumps. There were no red cells or casts. The spinal fluid was grossly bloody, formed a pellicle promptly and gave no bacterial growth.

On the second hospital day a second spinal fluid specimen showed essentially the same findings. The blood glucose determination was 100 mg. per 100 cc. of blood. The serum calcium was 12.3 mg. and the phosphorus 7.6 mg.

The muscular twitchings and vomiting persisted, the vomitus appearing watery and green tinged. Withholding oral feedings did not alter the symptoms. An attempted cisternal tap failed because of a prevailing opisthotonus. On the evening of the second day the infant received digitalis for apparent cardiac failure. Supportive therapy included oxygen, parenteral fluids and calcium chloride. Wangensteen suction was initiated in an attempt to relieve abdominal distension. The temperature rose to 100°F, but the subjective and objective symptoms increased in severity, the infant expiring on the third hospital day. Necropsy was performed.

DIFFERENTIAL DIAGNOSIS

Dr. Clifford J. Tichenor: This three week old newly born, previously in ostensibly good health, entered the hospital with the complaints of vomiting and muscular twitchings of approximately three days duration. The twitchings which were first noted in association with a slightly elevated temperature and irritability were found to be accompanied by a slight nuchal rigidity and a hyperextended back. The birth history had been perfectly normal and the family history was non-contributory. The anterior fontanelle was found to be bulging, the head circumference was within normal limits, the deep tendon reflexes were exaggerated and the superficial reflexes not elicited. There was uniform abdominal enlargement with positive fluctuation signs present, indicative of free fluid in the abdomen.

The blood count was not remarkable, but the urine was cloudy, showed albumen and many white cells in clumps. Spinal fluid and cisternal fluid was repeatedly bloody, apparently traumatic in origin since no mention is made of an attempt to centrifuge the fluid. The blood sugar was normal, but the serum phosphorus was quite markedly elevated. Digitalization was initiated for apparent heart failure.

The onset can justifiably be called abrupt, the course rapid, death occuring three days after admission. It seems clear that some acute process was going on and was localized to the abdomen and associated possibly with the genito-urinary system; or some intra-cranial process was going on, dependent or independent on abdominal localization. Apparently cardiac insufficiency was a terminal phase undoubtedly due to acute toxic myocarditis, and explainable as a circulatory complication.

What could have caused such an abrupt change of health in a newly born, associated with muscular twitchings and vomiting unrelated to food, and involvement of the central nervous system and urinary tract? Several things come to mind. Was this an inflammatory process? The infant was mildly feverish and prostrated, but the leucocyte count was little elevated. There was pus in the urine.

Intracranial birth injury (including the effects of anoxia and hemorrhage), and congenital defects of the brain are the most frequent causes of convulsions in very young infants, with acute infections (both intracranial and extracranial) and tetany occupying places of secondary importance. Far less frequent causes of acute convulsions in infants are spontaneous hypoglycemia, brain tumor, renal insufficiency, poisoning, asphyxia, spontaneous hemorrhage and postnatal trauma.

So-called febrile convulsions, at the onset of extracranial convulsions would not seem likely with the low grade temperature elevation reported. The diagnosis of intracranial infections such as acute meningitis, encephalitis, sinus thrombophlebitis and cerebral abcess would depend on the examination of the spinal fluid. Here we have no help, except perhaps from a negative sense.

Intracranial hemorrhage from birth or other trauma would have to be above the tentorium to produce a bulging, tense fontanelle. It should be remembered that cerebral edema could cause this phenomena and I am more inclined toward that explanation. There is nothing to suggest hemorrhagic disease of the newly born since this usually occurs in the first week of life, but the possibility of the rupture of defective vessels would be hard to discount. Again the nature of the spinal taps and grossly bloody fluid is equivocal. They could imply bleeding into the subarachnoid space. Some of the symptoms are those of increased intracranial pressure and involvement of the cerebral hemispheres. The most common conditions affecting the central connections of the oculo-motor nerves within the brain stem are vascular disturbances, with bulbar poliomyelitis, encephalitis and the various types of meningitis in secondary roles. Cerebral edema could also produce a temporary third nerve palsy.

The toxic causes for convulsions in the infant such as convulsant drugs, kernicterus and acute lead encephalopathy would seem ruled out by history.

Metabolic disturbances such as acute hypoglycemia and infantile tetany were eliminated by normal blood chemistry for sugar and calcium.

Intracranial congenital defects of the brain such as porencephaly, tuberous sclerosis and vascular anomalies are more prone to cause chronic or recurrent convulsions. Brain tumor, for example, a rapidly growing primary or metastatic neoplasm is an extreme rarity in this age group. It would seem, however, that we are not dealing with the more frequent causes of convulsions in the newly born.

As for the second presenting symptom, when vomiting, unrelated to food, occurs shortly after birth and is persistant, the possibility of some more serious disturbance must be considered. Vomiting is not an infrequent symptom of intracranial lesions which result in increased intracranial pressure, but again I mention that the signs and symptoms of cerebral edema may be similar to those of cerebral hemorrhage. Vomiting is also a constant manifestation of obstructive lesions in the digestive tract—being most frequent in the esophagus and intestines. The time of onset of symptoms in this infant's life and the negative intake relationship would seem to point away from the gastro-intestinal tract.

Turning again to the less frequent causes of convulsions in infancy, I should like to discuss the symptoms and signs of renal insufficiency. Pyuria may or may not exist—in this case it does. The blood inorganic phosphorus is elevated, as it is quite markedly here, the normal being considered 4.5 to 5.5 mg per 100 cc. and slightly higher in newly born infants. If this patient had a disturbance such as pyelonephritis it would account for the onset of fever, irritability, the central nervous manifestations of meningismus and convulsions and especially the gastro-intestinal disturbance vomiting. In uremia muscular twitchings are common and may be very painful. It is possible that there may have been such an origin as pyelonephritis, perirenal abcess, poly-cystic disease, calculi, tuberculosis, renal thrombosis or most likely in this age group some genito-urinary tract anomaly. Pus and albumin in the urine definitely demonstrates that renal parenchyma was involved.

Ascites is rare in infancy, renal and cardiac conditions being the ones most responsible. Other remote causes include portal obstruction, tuberculous peritonitis and splenic vein obstruction.

Since the infant received digitalis it must be assumed that there were symptoms of myocardial damage, although this is not clear in the case presentation. Overwhelming cardiac damage would cause rapid dilatation of the heart, a weak irregular pulse, enlargement of the liver and distension of the veins of the neck. Cyanosis and dyspnea would reflect in paired pulmonary circulation; none of these signs and symptoms are mentioned here. Vomiting might accompany an acute passive congestion

of the abdominal viscera and edema might indicate a disturbance of peripheral circulation and kidney damage.

The problems involved in this diagnosis cannot be complete without mentioning the possibility of miliary tuberculosis to explain the rapid declining course, the meningeal irritation and twitchings. Against tuberculous meningitis, pyelonephritis, peritonitis and myocarditis are the negative family history, the absence of an old tuberculin sensitivity report, the rapidity of onset and the absence of red blood cells in the urine.

In summary, this newly born patient was acutely ill, with evidence of intracranial pathology, renal pathology, and terminal circulatory failure, but little suggestion of an acute inflammatory process, certainly not an inflammatory process that was causing much of a systemic reaction attributable to infection. The temperature was only slightly elevated on one occasion and the white cell count was normal. Many pus cells in clumps were noted in the urine. Just what does this mean? There are three anatomical sources of pus in the urine—the urethra, the bladder and the kidney. The fact that albumin was noted indicated high infection, so that although it is reasonable to make the diagnosis of pyelitis it is difficult to trace its origin. It may have been of ascending nature. Statistically colon bacillus is the most frequent offender, especially in females, and genito-urinary tract anomaly would seem the most probable cause of pyelitis in this age group. There is no history of a preceding infection elsewhere. The nature and location of the urinary tract anomaly I would not attempt to state.

On the basis of the way the patient was handled in the hospital, I assume the condition was erroneously considered to be infantile tetany, and fruitless attempts were made to localize intracranial pathology. If the diagnosis had been intracranial hemorrhage, shock measures would have been employed and sedation used to control convulsive movements. Bleeding if present was apparently not sufficiently acute or severe enough to produce shock.

I exclude pyogenic meningitis on the basis of negative or traumatic spinal taps and symptomatology more referable to the genito-urinary tract. The unsatisfactory abdominal examination makes it difficult to discuss the anatomical and pathological possibilities in that region.

My diagnosis, therefore is renal insufficiency, associated with pyelitis, probably on the basis of genito-urinary tract anomaly, with uremia and terminal circulatory failure. The confusing cerebral manifestations I account for on the basis of cerebral edema. My second choice would be intracranial hemorrhage, circulatory failure and chronic passive congestion in the kidneys and other abdominal viscera.

Clinical Diagnosis: 1. Hypoglycemia. 2. Infantile Tetany. 3. Intracranial Hemorrhage with Meningitis? 4. Congenital portal obstruction?

Dr. Tichenor's Diagnosis: 1. Renal Insufficiency. 2. Intracranial hemorrhage.

PATHOLOGICAL DISCUSSION

Dr. Lois Murphy: The body was well developed, but poorly nourished and the abdomen was markedly distended. The fontanelles were patent and depressed. Approximately 5 cc. of yellow tinged cisternal fluid was obtained, the needle entering the cisterna magna 2.8 cm. from the skin surface. No gross pathological changes were observed in the brain.

The thymus gland weighed 4 gm. and had a pale atrophic appearance. The pleural cavities, mediastinal and bronchial lymph nodes appeared normal. The trachea and bronchi contained a small amount of gastric contents. The right lung weighed 50 gms. (normal 31 gms.) the left lung 45 gms. (normal 27 gms.), both being mottled in appearance, of varying pink to bright red in color. The red areas had a firmer consistency than the lighter ones and the cut surfaces showed moderate edema.

The pericardial sac contained about 10 cc. of clear, straw colored fluid. The heart weighed 22 gms. (normal 20 gms.) with normal measurements. The valves appeared normal and the ductus arteriosus and foramen ovale were closed. The right ventricular wall was 2 mm. in thickness, the left 9 mm. The myocardium was pale and flabby.

The peritoneal cavity contained 250 cc. of bloody purulent fluid, the exudate being especially thick in the dependent portions. There was a large cystic mass, orange-sized, in the right perirenal region and adherent to the ascending colon and inferior surface of the liver. This dissected mass was found to be a large perinephritic abscess.

The serosal surface of the gastro-intestinal tract was covered with varying amounts of purulent exudate. The cecum and ascending colon were firmly bound to the large mass on the right. The mesenteric lymph nodes were enlarged and hyperemic.

The right adrenal gland was embedded beneath a large blood clot at the upper pole of the mass. The right kidney was about normal in size but was compressed and pushed inferiorly by the large perinephritic abscess. The renal pelvis was found to be dilated and several calyces contained frank pus. The renal substance was thinned out in several areas, but no distinct connection between the pelvis and the abscess cavity could be demonstrated. The lower pole was markedly hemorrhagic in the cortical areas. The left kidney was mottled in appearance and there were several small areas where the capsule was elevated by small collections of pus. On section the pelvis and calyces were dilated and contained purulent material. There were a few irregular areas of necrosis and hemorrhage throughout the renal substance.

Both ureters were tortuous and dilated to approximately 5 times their normal size. They were patent throughout and entered the bladder normally. The bladder wall was markedly hypertrophied and the mucosa appeared hemorrhagic. Trabeculation was absent. At the bladder neck there were 2 folds of mucus membrane which extended backward from the vera montanum. The urethra was patent.

Postmortem cultures recovered E. coli from cisternal fluid, peritoneal fluid and heart's blood.

Microscopically the lungs were intensely congested and edematous and contained a large number of desquamated heart failure cells. The myocardium was normal except for some edema and swelling of the fibers. The liver was congested, the parenchyma being somewhat swollen. The spleen was intensely congested and hemorrhagic and the pancreas showed edema. The right adrenal gland contained a large hemorrhagic area. The cortical substance showed areas of vacuolation.

The kidneys were intensely and densely infiltrated by leucocytes of which polymorphonuclear forms predominated. There was marked degeneration of the renal structure, many tubules being represented only by poorly staining shadows. A number of glomerular capsules contained granular necrotic material, but some areas of rather well preserved structure were noted.

The gross examination of the brain after formalin fixation showed some discoloration suggesting hemorrhage in the periphery of the cortical substance. In general the brain tissue was normal except for some congestion. The pia mater was congested and showed a slight leucocytic infiltration. The picture suggested a mild inflammatory reaction and was diagnosed as acute leptomeningitis.

PATHOLOGICAL DIAGNOSIS

1. Congenital valve of the posterior urethra with:
   a. Hypertrophy of the bladder and cystitis
   b. Pyoureter, bilateral
   c. Pyo-nephritis, bilateral
   d. Peri-nephritic abscess, right.
2. Purulent peritonitis
3. Broncho-pneumonia.

DIETARY REQUIREMENTS DURING THE FIRST TWO YEARS OF LIFE

Dr. Luther Emmett Holt, Jr.*

When Dr. McLendon wrote asking me to speak on this topic, it seemed to me that there were two possible ways to approach the problem. I could discuss the familiar textbook data, such as the need for 100 calories per kilo body weight, that animals fats are better than vegetable fats, that many children need a little iron, etc. Instead I have been bold to assume that you are all familiar with that basic information ordinarily given to medical students, and will talk about some of the newer developments in nutrition. This information cannot be applied with certainty to the feeding of infants and children at the present time but will undoubtedly become very important during the next ten years.

In the first place, what about the question of calories? Is there any reason to modify our ideas about the quantity of calories infants require? Is under-nutrition or over-nutrition a serious problem? Probably in the past, when infant feeding was more difficult than it is today, under-nutrition was a very important problem. I think over-nutrition is probably a much more important problem today. The reasons for this are several. Infants are introduced to solid foods much earlier now than was customary a few decades ago. It is the rule now, rather than the exception, for cereals and vegetables to be started at the second, third, or fourth month. When these foods are added, very often the sugar in the milk formula is not reduced and as a result the child is receiving more carbohydrate calories. As a result the current crop of infants is more obese. No great harm need be expected from this, but there are a number of minor difficulties encountered in the over-nourished infant. The difficulties are generally manifest in the skin. Over-nourished infants have great rolls of fat, they frequently suffer from intertrigo, and for reasons we don't understand very well are more susceptible to eczema. Particularly in the infant fed large quantities of carbohydrate, the skin becomes more sensitive to the scratch test and shows a much more striking dermatographia. From my own observations I have no doubt that the incidence of eczema can be reduced sharply by reducing calories, and especially carbohydrate calories. The skin becomes less sensitive to the scratch test and dermatographia diminishes. I do not mean to imply that reduction in weight is the whole story in the management of eczema, but I am convinced that it is a very important factor.

* Professor of Pediatrics, New York University. Presented before the George Washington Medical School Graduate Assembly in Pediatrics March 26, 1946 at Children's Hospital, Wash., D. C.

Infection of the skin is also facilitated in the over-nourished infant. It has been shown that skin lesions in the rabbit resulting from the introduction of known quantities of staphylococci were much larger when the animals were over-hydrated or were fed a generous carbohydrate diet than when the animals had less water or reduced carbohydrates. We can say that the allergic reactivity of the skin is increased by the state of hydration. Furthermore allergic phenomena in organs other than the skin are increased by hydration. Anaphylactic shock and even asthmatic attacks can be reduced in their incidence, at least in experimental animals, by dehydration.

How can we reduce the appetite in children who tend to get over-nourished? It seems to me that the usual treatment, i.e. reduction of fat intake, is absolutely wrong. When a fat meal is fed, the emptying time of the stomach is delayed. When the diet is free from fat, the stomach empties very rapidly and consequently the child gets hungry again. He tends to eat cookies, crackers and what-not between meals, and ends up with a much higher caloric intake than would have been the case if fats were fed. I am told that in the German army there was a great deal of suffering from hunger because of the shortage of fat in the diet. I tried out this idea recently on an adult friend of mine. He lost 10 or 15 pounds in no time at all when he began eating cream and bacon and eggs for breakfast instead of just toast and coffee. I would like to recommend this regime if you encounter the problem of the obese child.

What can we do for the opposite problem, the case of the under-nourished child? Of course we must separate under-nutrition which is a result of disease because that is a different problem. In general, for the poor appetite I think we can apply the reverse therapy. In addition some artificial restriction of activity is desirable. I learned that trick from my father a number of years ago. He was caring for his grandson, my nephew, and this particular boy of about two or three was a very active youngster, running all over the place. He wouldn't gain weight and didn't have a particularly good appetite. When he was put in a play pen that he couldn't climb out of, his weight shot right up. When he was taken out of the play pen he stopped gaining immediately. Of course that sort of treatment doesn't have a wide range of applicability, but it is useful occasionally.

Now let's leave calories and come to the subject of proteins. The nutrition literature is full of protein studies at the present time. I think we are just entering an era when protein foods, supplements, etc., will be exploited in much the fashion that vitamins have been exploited in recent years. We will have to guard ourselves against the pitfalls that the salesman of trick protein products will place before us. We do not have much information on the amino acid requirements of the growing child. Nine of these acids are said to be essential to health, and it is probable that there are

others. In our Metabolism Clinic at Bellevue we are studying the problem at the present time by withdrawing one amino acid after another from the diet for short periods. One interesting observation we have made is that the withdrawal of tryptophane causes a reduction of nitrogen reserves and considerable nitrogen loss. When tryptophane is restored to the diet the nitrogen balance returns to normal. I hope that we shall soon know more about the protein requirements of the growing child.

At the present time, some sixteen firms are engaged in producing one or another type of protein hydrolysate and are recommending these products for all purposes. The question is, what is the need and what are the indications for protein hydrolysate? In the first place, if we have to feed parenterally, as in such condition as diarrhoea, pre- or post-operative treatment, etc., we should use hydrolysates rather than whole protein because protein is antigenic. Secondly, hydrolysates rather than protein should be given by mouth in conditions of failure of digestive enzymes. The most striking of these enzyme failures in pediatric practice occurs in cystic fibrosis of the pancreas, interfering with digestion of protein and absorption of Vitamin A. Protein hydrolysate given by mouth in this condition causes real improvement clinically and the laboratory shows real improvement in the nitrogen balance. Theoretically preparations of pancreas should make this approach unnecessary, but the pancreatic preparations we have now are only moderately satisfactory. The third indication for giving protein hydrolysates is in conditions of food allergy. When a child is found to be sensitive to milk, I think it is much more satisfactory to use a hydrolysate and to know there is absolutely nothing antigenic in the diet rather than to substitute soy bean or some other protein preparation to which the child may become sensitive. If we have definite proof of food allergy, I think it is desirable to use one of the hydrolysates. However, I think the frequency of food allergy is greatly overestimated. I have found that non-specific therapy, such as the substitution of fat for carbohydrate in the diet, often has a more pronounced effect than the removal of some suspected antigen from the diet. It has been shown that eczema occurring in infants who are definitely allergic to certain articles of diet can be strikingly improved by the isocaloric substitution of fats for carbohydrates when removal of the offending dietary antigen caused little improvement. However, I don't to give you the impression that removal of the offending protein is without value because I am sure that is not the case.

So I think we have three indications for the use of protein hydrolysate: when feeding parenterally for any reason, in permanent enzyme failure, and in allergy. And I think that those are the only indications for the use of hydrolysates.

Now, what are the objections to the use of protein hydrolysate? The

objections are two. In the first place, it appears that some of the essential amino acids are destroyed in the commercial preparation of protein hydrolysate. A lot of black muck settles to the bottom of the receptacle in which hydrolysis is carried out, and this material, of unknown composition, must be removed in one way or another. There is no doubt that this material comes from some factor which is nutritionally valuable. The second objection, emphasized by the recent work of Dr. Wooley at the Rockefeller Institute, is that certain peptide fractions are broken up by hydrolysis, and that these fractions have special nutritional value. One particular peptide complex, a polypeptide, was originally noted to be a growth factor for the streptococcus and was therefore called "strepogenin." This polypeptide is an important growth factor in animals and may well have its counterpart in human metabolism. It is present in milk but not in eggs. Only a limited number of proteins have been assayed as yet for this factor. It may prove to be as important as any "essential" amino acid. I would suggest that you follow this work on strepogenin because it is likely that it will prove essential in the human diet.

Another problem I want to take up with you is that of the loss of protein in disease. A good deal is being written about this at the present time, particularly in surgical conditions. A similar loss of nitrogen occurs in the urine in many medical diseases, such as measles, meningitis, pneumonia etc. This loss is quite variable but may continue for days or even weeks. Protein is administered in considerable quantities in an effort to combat this so-called "toxic destruction of protein" and to maintain nitrogen equilibrium. At the present time we don't know whether it is desirable or not to maintain an equilibrium. The obese individual apparently loses more nitrogen than the individual who doesn't have much superfluous tissue. This fraction of the body nitrogen comes out very easily but just where it comes from we do not know. It undoubtedly served some purpose in the body, but until we learn more about it I see little point in undertaking strenuous measures to replace it. In order to maintain nitrogen halance under these circumstances we have tó increase protein intake considerably above normal, and to do so undoubtedly places a strain on the liver and a good many of the enzyme systems of the body.

A few years ago we had an opportunity to study this problem. I was very much interested în studies being conducted elsewhere on the self-direction of diets. It had been shown that, under many circumstances, rats would select the diet that was most useful to them at the particular time. The pancreatectomized rat who had difficulty in utilizing sugar would turn to fats. The parathyroidectomized rat would eschew phosphorus and eat more calcium. All in all there were some 70 or 80 examples in which the majority of the animals would adapt their diets to various needs, merely as

a result of his own selection. We were working with a spontaneous infection that occurred in rats, apparently due to a streptobacillus. We passed this infection from rat to rat, and abscesses resulted in each animal. We then offered them a variety of foods to choose from, protein in one dish, fat in another, carbohydrate in another, minerals, vitamins, etc. We had ten different food containers for the rats to choose from. Without exception, the rats suffering from the infection refused protein. That was the one consistent thing they did. Some took fat, carbohydrate or other foods, but all refused protein. This experiment led me to wonder if it is so desirable to try to replace protein in the presence of infection. Of course maybe the rat isn't as good an animal as Dr. Richards thinks he is. At any rate, the question deserves a lot more study before the final answer is obtained.

Before leaving the subject of proteins entirely, I want to call your attention to some new work from the Rockefeller Institute. By electrophoresis these workers have shown that the beta globulin is low in the newborn infant. Now we have known for some time that the plasma proteins were considerably below the adult level until the child was about one and a half to two years old. We can vaccinate an infant with any one of half a dozen organisms and yet circulating antibodies cannot be demonstrated until the child is about two years old. It may be that the beta globulin is essential for the formation of antibodies, and that the child would be able to make his own antibodies if beta globulin were supplied. The preformed antibodies are present in the gamma globulin fraction and are present in the newborn infant by transfer from the mother. It is going to be interesting to watch the literature for more information about the beta globulin.

Let's pass now to fats. Is fat a dietary essential? It has been claimed that we can get along perfectly well without any fat at all. A good many years back a study was made in Vienna which indicated that the results on a fat-free diet were not so good, but it may have been because the fat soluble vitamins were not supplied. A few years ago, Dr. Hanson in Texas fed a child on a diet as nearly free from fat as he could make it from 3 months of age to 23 months. That child apparently had a congenital blockage of the lymphatic channels so that chyle entered the peritoneal cavity. All of the vitamins and other nutritional elements were supplied with great care. This child was particularly susceptible to skin infections and to eczema. We did a somewhat similar experiment in Baltimore a number of years ago. In one of these babies, every time fat was removed from the diet he would develop eczema and typical asthma. This tendency disappeared when fat was supplied. There is a lot of literature, some of which we can't altogether trust, indicating that fats may have some role in immunity.

There has been much discussion about the dietary ratio of fat to carbohydrate in the problem of colic in infants. It has long been taught that colic

and flatulence were a result of the fermentation of carbohydrates and that restriction of carbohydrates was therefore indicated. Certain studies in aviators during the war are probably applicable to this problem. Under conditions of reduced atmospheric pressure it was found that abdominal discomfort and cramps were much less if the diet contined relatively more fat. Thus the old theory is at least partially substantiated, although doubts still exist about the relationship of carbohydrate fermentation to colic in infants.

We come now to a consideration of carbohydrates and their role in nutrition. We are all aware that they make up an important source of energy. But what else do carbohydrates do that is important? One of their important functions is their detoxifying action, by coupling with various toxic substances. Possibly an even more important function is that carbohydrates feed the intestinal bacteria and that these bacteria are very important in nutrition. Beginning with Pasteur himself, knowledge has accumulated to show that a number of animals, including frogs, guinea pigs, rats and chickens, do not thrive when raised under sterile conditions, free of intestinal bacteria. Subsequently it has been shown that bacteria in the cecum of the rat can synthesize thiamine and riboflavine and other vitamins of the B complex. We have studied the problem in man and have found that substantial synthesis of vitamin B occurs as the result of the action of intestinal bacteria. This synthesis is greatly influenced by diet. For instance, dextri-maltose is a satisfactory food for the bacteria which produce thiamine and cane sugar is far less satisfactory. Thus we see that vitamin requirements are not absolutely fixed, but vary with the type of bacteria in the intestine and with the general nature of the diet. Some dietary substances, in fact, appear to destroy vitamins. There is a factor in raw fish which is apparently capable of destroying thiamine. There is evidence that corn contains a factor which actually destroys nicotinic acid. It has has long been suspected that a diet of corn predisposes to pellagra.

There are certain practical applications of this problem that we frequently overlook. Chemotherapeutic agents given by mouth cut down the growth of intestinal bacteria in a very striking way. This is especially true of streptomycin. We don't know what vitamins are produced by particular organisms yet, and therefore it is important for us to be on guard for deficiencies when chemotherapeutic agents are given by mouth.

Now I want to make a few remarks about the "trace elements" in nutrition. We all recognize the importance of iron in the hemoglobin molecule. It is well to point out, however, that we need iron for other purposes than the manufacture of hemoglobin. It is particularly needed for the formation of cytochrome C, a respiratory catalyst apparently present in every cell in the body. This substance is being studied clinically in certain nutritional

deficiencies by a group in Boston and they are obtaining very remarkable results. So this function of iron is probably very important although it has received little publicity up to the present time.

Other trace elements such as magnesium, manganese, and zinc are present in various enzyme systems in the human body and undoubtedly are important. Cobalt is apparently essential in cattle since animals receiving inadequate amounts develop anemia. This has not been proven to be the case in man. We have never thought much about these trace metals in our diet but perhaps we should. It appears that our diet has enough of these elements in it to save bothering about it. On the other hand, agricultural practices have a way of changing and our sources of food are continually being changed. It is quite possible that in the future, we may encounter deficiencies of these elements as a result of changing dietary habits.

There are a few topics that I don't know very much about that we ought to consider briefly. One is the relation between nutrition and resistance to infection. Nutrition is unfortunately a two-edged sword when it comes to infections. What is good for the host may also be good for the parasite but it doesn't always work out that way. Studies of body lice in rats and in man seem to indicate that if the host's diet is adequate the lice become unhappy and leave, but thrive if the host eats a bad diet. There is evidence to suggest that in poliomyelitis a diet which favors the host also favors the virus. This field will have to be worked out very carefully.

Another thing that is seldom considered is that an unbalanced diet is sometimes worse than an inadequate diet. There are circumstances, for instance, when an unbalanced protein mixture is worse than no protein at all. We have shown in rats that an unbalanced amino-acid mixture, one that lacked tryptophane, caused a sharper decline in weight than one containing no protein at all. There are indications that the same may hold true in the vitamin field, although this has not been too well worked out at the present time.

Now I think I have taken enough of your time. I haven't talked on what Dr. McLendon said I was going to talk on, but I did want to call your attention to the implications for pediatricians in some of the current studies in nutrition.

ROCKY MOUNTAIN SPOTTED FEVER TREATED WITH PARA-AMINO BENZOIC ACID

Case Report No. 73

Dr. Sidney Ross D. B. 46–7021

D. B., a 4 year old white female, was admitted to Children's Hospital on July 29, 1946 with the complaints of malaise and fever for 7 days duration and a rash of 5 days duration.

The child had been perfectly well until one week prior to entry at which time she was noted to have become listless and feverish. Forty-eight hours after the onset of the fever a rash appeared which had its initial distribution about the feet and ankles and progressed so that during the next two or three days there was a generalized distribution over the trunk, chest and upper extremities. Concomitantly the child complained of headache and muscular aches and pains in the upper and lower extremities and experienced considerable malaise. The appetite was poor and the child vomited on one occasion. The temperature remained elevated during the entire week prior to entry and the child during this interval appeared acutely ill.

The patient resided on a farm near Potomac Mills, Virginia. Ticks had been noted in this area and during the earlier part of the spring had been observed on the child and removed but none had been noted recently. The family used a spring and a well as the source of its water supply; there were no privies or seepage in the nearby adjacent areas. Raw milk, which was obtained from tuberculin tested cows, was used by members of the household. There had been no contact with rabbits or dead animals as far as known.

The past history and family history were non-contributory to the present illness.

Physical examination at the time of entry revealed a well developed, well nourished 4 year old white girl who appeared acutely ill but in no obvious distress. Her temperature was 104.8°, the pulse rate 140, and the respiratory rate 40. Her sensorium was clear but she appeared very irritable and was uncooperative. A discrete, macular papular rash which blanched on pressure was noted chiefly on the upper and lower extremities and the trunk. There were a few scattered lesions on the palms and soles. No tick were found in the hairy regions. The posterior cervical, axillary and inguinal nodes were small and shotty. The neck was supple and Kernigs and Brudzinski signs were negative. The heart and lungs were normal. The liver and spleen were not palpable. The motor and sensory modalities were in good order. Physical examination was otherwise negative.

In view of the clinical findings together with the known concentration of ticks in this area a provisional diagnosis of Rocky Mountain Spotted Fever was made.

Laboratory examination revealed a hemoglobin of 10 gms. with 3.5 million red cells; the white cell count was 8400 with 55% neutrophiles and 45% lymphocytes. The urinalysis was essentially negative. Blood culture was negative as was the Wassermann and Kahn. A Weil-Felix agglutination test with Proteus OX19 on July 29, 8 days after the onset of illness, was positive in a dilution of 1:20. Five days later the titer had risen to 1:640.

Throughout the first two days in the hospital the child remained acutely ill with the temperature spiking between 100° and 104.5°. Drowsiness and irritability were marked and the child's appetite remained poor. The rash which had become more petechial now involved the entire thorax and abdomen. During this time supportive measures including antipyretics and an intravenous infusion of 300 cc. of 5% glucose in saline were administered.

On July 31, forty eight hours after admission,para-amino benzoic acid therapy was started. The dose was 1½ gms. initially and then ¾gm. every two hours thereafter. On the following day, the dose of para-amino benzoic acid was reduced to ½ gm. every 2 hours and this dosage was maintained throughout the remainder of therapy. The drug was administered orally in 15 cc. of chilled sodium bicarbonate solution (5%) and was well tolerated by the patient. Frequent para-amino benzoic acid blood levels were taken one hour following the previous dose and revealed the blood level to range between 20 and 25 mgms.%.

Two days following initiation of para-amino benzoic acid therapy a rather definite improvement was noted. The patient appeared less toxic, was considerably more alert, and her appetite improved. However, the temperature continued to spike during the next 5 days ranging between 100° and 102°. On the 6th day of para-amino benzoic acid therapy the temperature dropped rapidly to normal. By this time the rash had already begun to fade and the patient was asymptomatic. The child remained afebrile during the remainder of her hospital course. Her recovery was complete and she was discharged on the 17th hospital day after an uneventful convalescence. (Fig. 1)

Para-amino benzoic acid had been administered for 10 days during which time the child received a total of 55 grams.

Daily white counts obtained during the course of drug therapy to determine its leukopenic effect revealed a definite granulocytopenia and leukopenia one week after the initiation of para-amino benzoic acid therapy; the white count at this time was 3500 with 16% neutrophiles. However, the white count returned to normal when the para-amino benzoic acid was

discontinued. Similarly hepatic function tests obtained during the course of PABA therapy to determine any possible untoward effect on the liver showed a prothrombin time of 50% of normal, total protein of 6.9 gms.% and a 4 plus cephalin flocculation. Follow-up liver function tests are now being obtained.

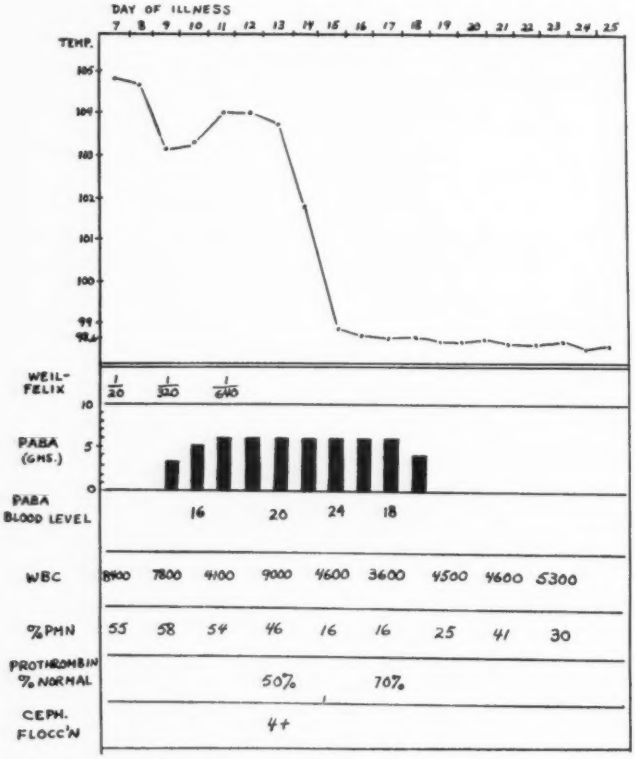

FIG. 1. Summary of patient's course

DISCUSSION

Dr. Sidney Ross: Following initial encouraging experimental and clinical reports of the value of para-amino benzoic acid therapy in endemic typhus, louse borne typhus and Tsutsugamushi fever, it was deemed of considerable interest to treat a case of Rocky Mountain Spotted Fever with this drug.

The dosage used in the reported cases in adults varied from an initial 4-8 gms. followed by 2-4 gms. every 2 hours. In this child, however, it was thought advisable to use between 1-2 gms. initially and then ½ gm. every 2 hours thereafter. With this dose it was found possible to maintain a satisfactory blood level of para-amino benzoic acid ranging between 15-20 mgms.%. In this connection it is not possible at the present time to define categorically what constitutes the optimal para-amino benzoic acid blood level. The object of the neutralization of powdered para-amino benzoic acid with 5% sodium bicarbonate was to render the mixture slightly alkaline and thus lessen gastric irritation. The child tolerated the drug in satisfactory fashion and no vomiting was encountered. The blood levels were performed in a similar fashion to that used for determination of blood sulfonamide levels.

A moderate leukopenia was the chief untoward effect noted in this case and on discontinuation of the para-amino benzoic acid the white-count rapidly returned to normal. It is important to perform daily white and differential counts while para-amino benzoic acid is being administered. No change was observed in the red count and hemoglobin. The effect of para-amino benzoic acid on the liver is somewhat controversial. In this case the prothrombin time was 50% of normal and the cephalin flocculation test was 4 plus. However, this may have been due to the effects of the disease per se rather than to the drug. Further investigation is necessary to clarify this point. A good urine output was initiated in this patient before para-amino benzoic acid was started in order to forestall the possibility of producing excessively high blood levels. There is no evidence that the drug produces kidney complications in a fashion similar to sulfonaminde drugs which in their chemical configuration are closely related.

It is difficult to evaluate precisely whether para-amino benzoic acid exercised any salutory effect on the course of the disease in this patient. Yeomans has reported that the best results in louse borne typhus were obtained when the drug was started on the 2nd and 3rd days of illness and observed some effect when the treatment was begun as late as the 7th day. It is apparent that much more extensive experience with para-amino benzoic acid would be required to find the limits within which beneficial effects may be expected but it is apparent that early treatment is extremely important. In view of the fact that therapy was started 9 days after the onset of the illness, one would expect less striking results in this case. It was observed that following initiation of para-amino benzoic acid therapy the child seemed to improve clinically within 48 hours as indicated by lessening of the drowsiness and toxicity and a general clinical improvement. The temperature, however, remained elevated during the next 5 days. It is hypothetical as to how long this patient's temperature would have

remained elevated without any specific therapy. Had the treatment been initiated earlier it is possible that a more prompt response might have been observed.

It would seem that para-amino benzoic acid in Rocky Mountain Spotted Fever does not act in rapid fashion. The drop in temperature does not parallel that obtained with chemotherapeutic agents such as sulfonamides and penicillin when used against bacterial infections. Yeomans has stated that the hypothesis which best fits the sequence of events in para-amino benzoic acid therapy is that the drug inhibits the multiplication of rickettsia inside the cells possibly by modification of the enzyme systems, thereby permitting the immune mechanisms of the body to dispose of them whereupon the vascular lesions begin to heal.

During the past summer all 6 cases of Rocky Mountain Spotted Fever diagnosed at Children's Hospital have been treated with para-amino benzoic acid. Ideally it would have been desirable to have treated alternate cases with this drug employing the untreated cases as controls. However, the number of cases were too few to permit any significant statistical evaluation. The results obtained in these 6 cases will be discussed at a later date.

Dr. Paul K. Smith:* Since Snyder *et al.* demonstrated in 1942[11] that oral para-amino benzoic acid reduced the mortality of white mice infected with murine typhus there have been several studies showing that this drug was effective in other rickettsial diseases. Grieff and co-workers [4], using infected yolk sacs demonstrated that para-aminobenzoic acid was effective against the organisms of epidemic and murine typhus fever. A moderately high concentration was remarkably effective in preventing the growth of the organisms responsible for murine typhus fever[4]. Hamilton[5]demonstrated that the rickettsiae of Rocky Mountain spotted fever were inhibited in chick embryos by para-amino benzoic acid in about one half the concentration that was required to inhibit the growth of rickettsiae responsible for murine typhus fever. He did not demonstrate any appreciable effect on the organisms of tsutsugamushi fever. No favorable action could be demonstrated by such closely related compounds as para-amino acetophenone, para-amino phenylacetic acid, para-amino cinnamic acid or 4-amino-1-napthoic acid. Murray *et al.* [6] demonstrated that, when used in large doses, para-amino benzoic acid was effective in reducing the mortality of gerbilles infected with tsutsugamushi disease (scrub typhus) if the drug was given both orally and parenterally. Anigstein and Bader[1] [2] demonstrated that the drug was effective when fed to guinea pigs infected with Rocky Mountain spotted fever.

* Department of Pharmacology, George Washington University School of Medicine, Washington, D. C.

The first use of para-amino benzoic acid in human infections was in louse borne typhus fever. Yeomans and co-workers [13] demonstrated a striking reduction in mortality of patients treated with large doses of para-amino benzoic acid. They stressed the need for beginning the treatment early for best results and emphasized that large doses were required. They gave four to eight grams as the initial dose and two grams every two hours unless they obtained excessive levels.

They observed that with blood levels above 40 mgm. percent of the drug, two of the patients became drowsy and delirious. There was some evidence that the white count was diminished and they stress that this should be observed in the future use of the drug.

Although there have been no further published reports of the use of the drug in epidemic typhus fever, there has been one study of its use in endemic (murine) typhus fever [9]. In this study, 29 patients were treated with para-aminobenzoic acid, usually given in a dose of two grams every two hours along with sodium bicarbonate. The patients recovered on the average more quickly than patients not receiving the drug. The effects are more difficult to evaluate in this disease than in the epidemic typhus fever because the mortality rate is relatively low, but it was demonstrated that the duration of fever was significantly less in those receiving the drug than in those receiving any other method of treatment.

So far there has been only one case report [7] of a patient treated with para-aminobenzoic acid who was infected with spotted fever. This was a forty-six year old woman who had been ill three days. Para-aminobenzoic acid was begun thirty-six hours after her admission into the hospital. The response of the patient was very rapid to treatment. Obviously further work in this connection is needed.

Realizing that large doses of para-aminobenzoic acid might be needed for the treatment of human infections of scrub typhus, since quite large doses had been required in experimental infections, Tierney [12] gave eight grams of the drug initially and then three grams every two hours to patients until their temperature had been normal for one week. With this large dose they obtained levels of 30 to 60 mgm. percent of the drug in two days. The only toxic effect observed was a slight confusion in some patients. There were eighteen patients treated with the drug and sixteen alternate untreated patients. The results of treatment were very encouraging. The only toxic effect observed was a low white count of less than three thousand in two patients near the end of treatment.

It is obvious from the above that para-aminobenzoic acid shows promise of being an effective chemotherapeutic agent in rickettsial diseases. It should be stressed, however, that the number of patients that have been treated is quite small and much more work needs to be done to demonstrate

whether the drug is effective under all conditions. Further, since the drug may be employed in very large doses over a relatively long period of time it will be necessary to evaluate its possible toxic effects very carefully. So far the diminution in white cell counts that have been observed have not proven to be serious and have subsided soon after treatment ceased. Nevertheless, remembering experiences with such drugs as thiouracil, it is well to withhold judgment as to whether or not trouble can be expected from that source. Certainly it is well to do frequent total and differential white counts and to discontinue the drug if the total white count falls to three thousand or less per cu. mm.

It will be remembered that para-aminobenzoic acid actively inhibits the chemotherapeutic action of sulfonamides and it is obvious that it can not be employed at the same time any of these drugs are being employed. There is however, no reason to believe that it interferes with the therapeutic action of penicillin, and the employment of penicillin with para-aminobenzoic acid is not contra-indicated, and may in fact be necessary with the late complications often seen with the severe rickettsial diseases.

The mechanism of action of the drug is but little understood. Zarafonetis and co-workers have shown [14] that animals infected with scrub typhus and treated with para-aminobenzoic acid are immune to the disease after recovery. This suggests that the drug is only rickettsio-static.

Pharmacological studies have shown [10] that para-aminobenzoic acid is very rapidly absorbed, high plasma levels being obtained within one hour after oral administration of the drug. It is also very rapidly excreted and two hours after an oral dose of the drug, the plasma levels may be much lower than one hour after the drug is given. This is important from the standpoint of laboratory control of the administration of the drug, since a blood sample taken for analysis shortly after the drug is given may give a much higher value than one taken two hours after a dose of drug. Thus it is important to know at what time the blood sample was taken with respect to the last dose of the drug in order to evaluate whether the plasma level is unduly high. The drug is conjugated to a large extent with glycine, presumably in the liver, and excreted as para-aminohippuric acid. This suggests that patients with liver damage may have difficulty in detoxifying the drug, and also suggests that the drug might be useful as a liver function test since it can be determined quantitively in the laboratory with much greater ease than hippuric acid is determined in the ordinary benzoic acid liver function test. Further work on this point is in progress. The drug and its degradation products are readily excreted by the kidneys [3] and some are actually secreted by the renal tubules [8], suggesting that the danger of renal irritation is not as great as with the sulfonamides.

SUMMARY

There is preliminary evidence that para-aminobenzoic acid may be a valuable therapeutic agent in the treatment of most of the rickettsial diseases. For effective therapy the drug should be given in large doses (2 or 3 gms. every 2 hours with sodium bicarbonate) early in the disease and continued until the temperature has returned to normal.

Although no serious toxic effects have been reported from its use the patients should be followed carefully for possible reactions, especially those affecting the leucocytes.

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TICK PARALYSIS

Case Report No. 74

Dr. Ralph Stiller C. W. 46–6924

C. W., a 2½ year old white female, awoke on the morning of July 25, 1946 complaining for the first time of difficulty in walking. She had no fever. Her local physician advised bed rest but 24 hours later suggested that she be hospitalized as drowsiness and moderate disorientation had supervened. She had had no difficulty in maneuvering her arms, trunk or head. There had been no change in the character of her speech, no complaints of pain, no difficulty with deglutition. Just prior to admission to the hospital she had had one bout of vomiting.

Past history revealed that the child had been unusually well. She had had measles one year prior to the present illness. She had a normal delivery after an 8 month period of gestation, weighing six pounds at birth. The family history was negative for any inheritable chronic diseases. It was ascertained that the area in which the child lived was infested with ticks but that there was no history of her having been bitten recently.

Physical examination on admission revealed an afebrile, well developed, well nourished white female, lying quietly in bed unable to stand, yet with a strong and active kick. She could not sit up with ease though she did manage to pull herself erect. She did not have a "poker back." Her neck was quite flaccid and she had some difficulty holding up her head. Neurological examination showed absent deep reflexes. The abdominals were not elicited but the gag reflex was present. There was no lateral deviation of the uvula. Babinskis bilaterally showed plantar flexion. The upper extremities were ataxic as evidenced by ineffectual attempts at grasping with overshooting before this was successfully and clumsily done. Examination of the eye grounds revealed hyperemic and blurred fundi. The discs were not visualized.

A tick was found embedded in the left parietal region of the scalp and the regional posterior occipital lymph nodes were enlarged. The tick was later identified as a female Dermacentor andersoni. Remainder of the physical examination was entirely negative.

Blood count revealed a hemoglobin of 13 grams, 3,900 leucocytes of which 46% were polymorphonuclear cells and 54% lymphocytes. Urinalysis was negative. A spinal tap was done on admission. The fluid was clear, under no increase of pressure and showed less than one cell per cubic mm. Protein was 5 mg. percent, sugar 30 mg.%.

The child remained afebrile throughout her hospital stay. There was a

dramatic subsidence of the neurological symptoms following removal of the tick and she was discharged 12 days after admission completely well.

Discussion

Tick paralysis has been known to occur not too rarely in Northwestern United States, Southwestern Canada, South Africa, Australia and Crete. The vectors vary depending on the locale. This case is being reported primarily because of its rarity in the Eastern United States. In western parts of the country sheep are most commonly attacked, the vector being Dermacentor andersoni. This was the same vector that was found in this case although most commonly in the east Dermacentor variabilis is the offending species.

The case just presented was typical in many respects. The onset is usually sudden, the first alarm occurring when a previously normal child awakes in the morning either unable to walk or, if able to get about, markedly ataxic. The flaccid paralysis gradually ascends eventually causing upper extremity ataxia and finally, if not checked, resulting in respiratory paralysis and death. There may be pupillary dilatation and nystagmus. There is usually no fever. Diarrhea and convulsions have been known to occur.

The symptoms usually occur 9 to 16 days after the tick attaches itself to its host and immediately begin to abate with removal of the tick. This fact has led to the postulation of a toxin elaborated by the tick as the etiology of the paralysis. And indeed it is hard to conceive of a virus etiology that would square with this recovery coincident with removal of the tick. Ticks vary in their toxin producing ability. Many either elaborate no toxin or elaborate too little to produce symptoms. The condition is rare in humans over the age of ten, a fact which tends to agree with the postulation that the toxin is not secreted in sufficient quantity to affect any adults but the aged. There is no apparent difference in the course of the disease caused by different species of ticks. It is felt that the toxin is elaborated in the salivary glands of the tick. However it is known to be present in the eggs and the disease is often more severe if the tick is pregnant. Paralysis is also more severe if the place of attachment is near the neck or spinal column.

Death has occurred from respiratory paralysis. Pathological examination has not yielded too distinct an entity. Primarily the picture is one of congestion with punctate hemorrhage around the nerve cells of the lower motor neurones and cranial nerves. There is extensive myelin sheath destruction. Perivascular infiltration is present associated with an excess of mononuclear cells.

Treatment consists in prompt removal of the tick. Care should be taken

not to let the mouth parts remain in situ and in some cases it may be necessary to excise a small area at the site of attachment. In extracting the tick the forceps should be applied near the head so as to avoid undue squeezing which may result in the injection of more toxin into the patient. Application of a drop of turpentine to the tick may cause it to back out intact. It is very important to search the patient thoroughly for multiple infestation and not to be satisfied with locating and removing one tick. In those cases caught late that may be showing respiratory difficulty, a respirator may be indicated but care must be taken not to put the child in a respirator until it is absolutely necessary.

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PARATYPHOID FEVER SIMULATING ACUTE APPENDICITIS

Case Report No. 75

Dr. Charles Stiegler R. C. 46–7098

R. C., a 10 year old white male, was admitted to Children's Hospital on July 31st because of abdominal pain of 2 days duration. The patient, a native of Minneapolis, had been on a trip with his mother for a month prior to admission. They had set out by steamer through the Great Lakes, stopping overnight at several Canadian ports. This was followed by a train trip to Washington, with stopovers at New York City and Philadelphia.

Two days before admission, the patient had a slight chill and fever followed by one loose stool. At this time he complained of moderately severe generalized abdominal pain and vomited once. The pain soon became less severe but persisted throughout the following day, as did the low grade fever. There was no further vomiting, and the patient did not have any bowel movements. At 2:30 a.m. on July 31st, the patient awoke with severe generalized abdominal pain, with some localization of the pain to the right lower quadrant. He was nauseated and vomited several times. The temperature was 102°. Examination of the abdomen at this time revealed generalized tenderness, more marked in the lower half of the abdomen on the right side. There was mild rebound tenderness. The abdomen was not distended but there was a mild, doughy tension throughout. There was moderate voluntary spasm in the right lower quadrant and more in the left lower quadrant. The rectal examination revealed generalized tenderness, more marked on the right; no masses were felt, and there was no blood on the examining finger. A white blood count showed 13,000 leucocytes per cu.mm., of which 84% were polymorphonuclears. The patient was then admitted to the hospital for observation, as a possible acute appendicitis.

The temperature on admission was 102.6°. The physical examination on admission was unchanged from that recorded above. The leucocyte count, repeated on admission, showed 7,900 leucocytes per cu. mm. An appendectomy was performed. A Meckel's diverticulum was also found and removed. The appendix measured 5.5 x 1.5 cm., with slight congestion of the external surface; on section, there was nothing of note except slight dilatation of the distal end.

Following the operation, the patient ran a sustained temperature for 8 days, ranging from 100° to 104°. There were repeated bouts of nausea and vomiting for 3 days postoperatively. The generalized abdominal pain

persisted for 7 days. There was no evidence of surgical or pulmonary complications during this period. There was no rash, and successive urinalyses were normal. A leucocyte count of 6,000 was obtained on August 2nd, with a differential of 75 neutrophiles, 24 lymphocytes, and 1 monocyte. An agglutination test with febrile antigens was negative on August 5th. The patient had 5–6 loose, watery brown stools daily on August 5th, 6th and 7th. Stool cultures taken August 8th and 9th failed to demonstrate any pathogenic organisms. Penicillin therapy was administered August 6th to 8th without response; penicillin was discontinued at this time and sulfadiazine therapy begun. The temperature returned to normal within 36 hours, remaining so until discharge. The blood count was repeated August 9th, showing 12,900 leucocytes with 76% neutrophiles. The patient showed rapid subjective improvement, and was continued on sulfonamide therapy until discharged August 14th.

During his last week of hospitalization, the patient's mother volunteered the following information that she had received in response to a letter home. While working in a defense plant in 1944, the mother had been immunized against the Typhoid-Paratyphoid A and B group of organisms. On the day of discharge, serum taken from the patient showed agglutination with E. typhosa "O" dilutions 1:20–1:160, with E. typhosa "H" dilutions 1:20–1:40, and with Paratyphoid B dilutions 1:20–1:1280.

Discussion

Dr. William Howard. The diagnosis of a sporadic case of paratyphoid fever of the A or B variety is usually suggested by the clinical picture and the course of the illness, and is verified by laboratory aids. When abdominal pain becomes the outstanding symptom at the onset of the illness, there is insufficient time to assemble evidence in favor of an enteric infection. In this instance the magnitude of the abdominal signs made surgical exploration mandatory, with every expectation of discovering an involvement of the appendix. The findings at operation and the subsequent course left no doubt as to the presence of some other disease to account for the patient's symptoms. A rapid review of these symptoms was sufficient to remind the observer that the same clinical picture was present before and after operation, and was little influenced, for better or worse, by surgery. The first hint of gastro-intestinal pathology wss the persistence of the nausea, which was then followed by a diarrhea which lasted for 72 hours. A tentative diagnosis of enteric infection due to some member of the typhoid-colon-dysentery group was then made, but was not substantiated until positive agglutination reactions were obtained on the day of discharge.

The predominance of abdominal signs and symptoms in this child is noteworthy. The pathology of paratyphoid fever is similar to that of typhoid,

with involvement of lymph follicles, Peyer's patches and mesenteric glands. Such localization of pathology is sufficient to account for the variable abdominal findings which are reported, and for the occasions when symptoms and findings may simulate appendicitis. In another case personally observed under similar circumstances there was free fluid in the peritoneal cavity and involvement of the appendix. Culture of the peritoneal transudate yielded a luxuriant growth of Eberthella typhi. In the present case, all signs pointed to an acute abdominal episode, and there was ample evidence to sustain the opinion that peritoneal irritation was present. Microscopic examination of the apparently normal appendix might have given additional information relative to the involvement of that organ.

Splenomegaly was absent in this patient, but is normally uncommon in paratyphoid infections. At no time was there any evidence of either of the two types of roseolae which usually occur on the skin of the paratyphoid patient. The initial leucocyte count in this instance was elevated, a more or less frequent finding in paratyphoid fever as compared to the characteristic leucopenia of typhoid infections. Leucocytosis is especially in clined to occur in the gastro-intestinal form of paratyphoid infections in young children.

Recovery took place rapidly immediately after the administration of adequate doses of sulfadiazine, and this appeared to be a direct response to the chemotherapy.

With his Odyssey through the Great Lakes and the Northeastern United States behind him, it was well nigh impossible to retrace this patients steps to determine the source of his infection. In spite of the fairly short incubation period of paratyphoid (usually less than ten days) there were a number of places where exposure might have occurred, including steamers, ports, hotels, trains and restaurants. It is comforting to assume that the mother escaped a similar infection because of her previous immunization against the organisms of the typhoid paratyphoid group, an assumption which might have been strengthened by the performance of agglutination studies on her serum. Nevertheless, such instances serve to indicate the importance of immunization against these organisms, especially in individuals who must travel extensively or be in areas where water and food supplies cannot be adequately controlled.

Dr. John H. Lyons. Acute appendicitis is so common in children, and perforation such a serious complication that it is a sound policy to operate and explore the appendix in any acute abdominal attack in a child when that organ can not be eliminated as the causative factor. Under this plan of procedure, it is inevitable that a certain number of cases will be operated on needlessly. The case just presented typifies this group. There were several points in the clinical picture that were at variance with the classical

description of acute appendicitis. In the first place, the patient had a chill and a loose stool at the onset of the attack; in the second place, his leukocyte count just before operation was 7,900 per cu. mm., even though his temperature was 102.6. In spite of these discrepancies his overall picture was certainly strongly suspicious of acute appendicitis. He was therefore operated on and a normal appendix and an uncomplicated Meckel's diverticulum removed. As stated before, the patient had a stormy convalescence and it was thought for several days that some surgical complication had arisen. It was not until approximately one week after operation that it was realized that the patient's symptoms were due to the same condition that he had before operation; and it was not until the day of his discharge that the solution of the problem was reached with the report of the positive agglutination test for Para-typhoid B. If against the cases operated on unnecessarily under the policy of operating on suspicion of acute appendicitis are balanced the morbidity and mortality caused by waiting until a definite diagnosis can be made, the conviction remains that the policy is a sound one.

CHOLESTEATOMA

Case Report No. 76

Dr. Lois Murphy D. B. 46–1570

D. B., an 8 year old white female was admitted to the Children's Hospital on July 5, 1946 because of a swelling above the right ear. The parents had been aware of this mass for eight months. During the last three months the tumor had become larger, indurated and caused pain in the right side of the head and right ear.

The patient's birth history was normal. She had had measles at 3 years of age and mumps at 6. She had adenoids and tonsils removed in 1944. There were 3 siblings and the mother and father were living and well. There was no known history of familial disease.

The patient was a well developed white girl who did not appear acutely ill. A tumor mass was present on the right parietal area of the skull. The mass was about $3\frac{1}{2}$ cm. in diameter. The tumor was indurated and tender on palpation and was slightly nodular. There were no other unusual physical findings.

An x-ray examination of the skull in the antero-posterior and lateral positions revealed the presence of a rounded area of decreased density in the right parietal bone measuring about 3 cm. in diameter. This area was surrounded by a thin zone of increased density excepting for a small space in the anterior border. Immediately below and anterior to it there was another small area of decreased density measuring about 0.5 cm. in diameter. The inner table seemed to be intact but was displaced somewhat inward while the outer table and the diploe were destroyed and protruded externally. The outer table was markedly thickened and there was some swelling of the overlying soft tissue. No change had occurred in the x-ray findings between March, 1946 and July, 1946.

At operation, July 18, 1946, a horseshoe flap was turned down over the mass in the right parietal bone. When the scalp was reflected, a bluish, cystic, fluctuant mass was seen. Four burr holes were made and the mass was removed in its entirety. As the bone was lifted out, a portion of the inner plate was seen to be eroded, a whitish mass protruded and was attached to the dura. This area was excised. The underlying brain was normal in appearance. The outer layer was grooved and a tantalum plate was fitted over the defect. Fibrin foam covered the dural defect. The plate was held in place by 3 tantalum screws. Nitrous oxide, oxygen and ether constituted the anaesthetic.

The microscopic section was made from a particle of squamous epi-

thelium in irregular folds with attached connective tissue and was reported by Dr. J. Lindsay as showing considerable superficial keratinization and desquamation of epithelial cells in the folds. More deeply there were small cyst-like spaces filled with desquamated cells. The histological picture was that of cholesteatoma. Nothing in this material was suggestive of malignancy.

The child's recovery was uneventful. Because of sensory seizures which developed postoperatively, she was given 1.5 grains of sodium dilantin three times daily.

Discussion

Cholesteatoma is a tumor mass, usually cystic, which is composed of a lamellated, waxy material surrounded by a wall resembling stratified squamous cells. The fatty material may contain various lipids almost always including cholesterol. The outer layer is practically avascular giving the structure a pearly color. The only growing part of the tumor is the external layer which is attached to surrounding structures; this characteristic along with the extremely friable nature of the tumor, makes removal difficult and recurrences frequent. Cholesteatomas or epidermoids of this type occur within the bones of the calvarium, all parts of the brain, ventricles and basal regions usually near the midline and regularly are connected with the meninges. The origin most probably is embryonal epidermal inclusion or dyshistogenesis. The embryonic rests occur as remnants from an incomplete separation of the neural from the surface ectoderm. Their location beneath the scalp, within the diploe, between the bones and dura, beneath the arachnoid membrane base and in the ventricles depends on the depth at which the incomplete separation occurs. The embryonic age determines whether the tumor will become the simple epidermoid or the more complex dermoid. There is some evidence in isolated cases that trauma is an etiological factor; endothelial structures or ependymal epithelium may be associated with formation of cholesterol containing epidermoids.

Growth of a diploic epidermoid causes the tables to be pushed apart with absorption of the inner, outer or both tables but usually the inner. The x-ray picture is so characteristic that the diagnosis is usually made by the roentgenologist. When the inner table is involved, the appearance is scalloped and has a clear cut margin which is denser than the surrounding bone. The outer table appears completely eroded, the opening thus produced being quite evident on stereoscopic examination. When the outer table is involved, the margins are more likely smooth and not scalloped. The marginal view reveals some separation of the two tables of the skull.

The typical history is that of a swelling of the scalp usually over a long

period of time and a defect of the skull which may occasionally be palpated or may be demonstrated by roentgenograms. Intradiploic epidermoids rarely give neuological symptoms. However, convulsions, headache and impaired vision have been reported. The tumor is soft, fluctant and may pulsate.

FIG. 1. Epidermoidoma (Cholesteatoma) of right parietal bone. Note sclerotic border surrounding the rounded area of decreasing density which is characteristic of this tumor. The small area where this zone is lacking proved to be an attachment of the tumor to the dura.

The first case of diploic epidermoid was described by Muller in 1838 and he introduced the name cholesteatoma. Bailey and Esmarch in 1920 described a case of the frontal bone involvement treated with surgical excision. Bucy reviewed 13 cases of diploic epidermoids up until 1935 and added 3 cases. The ages of onset of these 16 cases varied from 2 to 49 years. The age of operation varied from 16 to 70. In 1943 Rand and Reeves described 11 additional cases treated surgically. There have been other

isolated cases reported. However, the diploic cholesteatoma is relatively rare. Cholesteatomas as a whole constitute .6% of brain tumors.

The surgical importance of this tumor lies first in differentiating it from meningiomas and sebaceous cysts of the scalp. In the case of the latter, all excised sebaceous cysts if examined histologically will be found to have a secretory type of epithelium. The epidermoid has a stratified type of epithelium with kerato-hyalin granules. It is also important that the diagnosis be made early, before the mass has become attached to numerous surrounding structures. It is of utmost importance that the entire layer of epithelium be removed. A small remaining fragment will cause a recurrence. It is for this reason that Cushing recommends the excision of a portion of the surrounding bone. The other important consideration is examination of the dura underlying the inner table because of the frequency of a meningeal attachment as was found in this patient. Occasionally some atrophy of the underlying cortex occurs.

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